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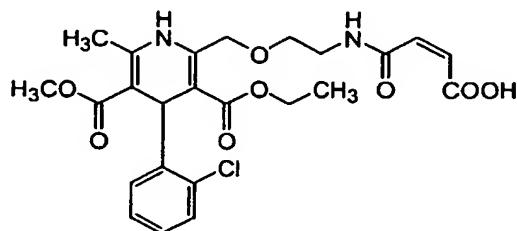
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(54) Title: AMIDE DERIVATIVE OF AMLODIPINE



(1)

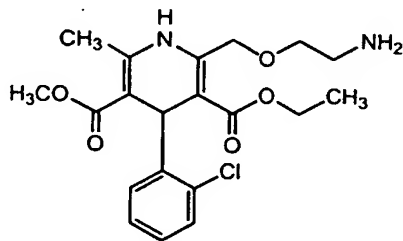
(57) Abstract: A derivative of amlodipine having the following formula is useful as pharmaceutical, either alone or in combination with amlodipine, in treating angina and hypertension.

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AMIDE DERIVATIVE OF AMLODIPINE

5 The present invention relates to a novel compound, to processes for preparing it and to its use in treating medical disorders. In particular the present invention relates to a novel derivative of Amlodipine.

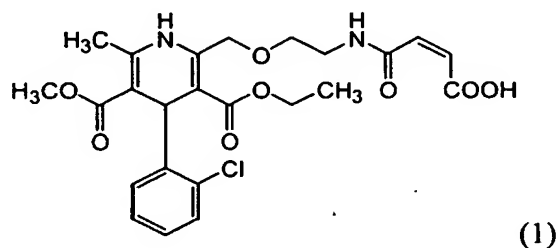
Calcium channel blockers (calcium antagonists) are useful in treating cardiac conditions including angina and/or hypertension. Dicarboxylate-dihydropyridine derivatives are generally known to possess calcium channel blocking activity. For
10 example, EP 089 167 and corresponding US 4,572,909 disclose a class of 2-amino group, 3,5-dicarboxylate dihydropyridine derivatives as being useful calcium channel blockers. These patents identify that one of the most preferred compounds is 2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-3-ethoxycarbonyl-5-methoxycarbonyl-6-methyl-1,4-dihydropyridine. This compound, which is now commonly known as
15 amlodipine, has the following formula:



Amlodipine exhibits good bioavailability and has a long half-life in the body.
20 While a variety of acid addition salts are taught in these patents to be suitable, the maleate salt is identified as the most preferred acid addition salt. However, the commercial product of amlodipine (NORVASC by Pfizer) uses amlodipine besylate (benzene sulfonate) and not amlodipine maleate. Indeed, subsequent patents EP 244 944 and corresponding US 4,879,303 indicate that the besylate salt provides certain
25 advantages over the known salts including good formulating properties. Apparently, amlodipine maleate suffered from tableting and stability problems so as to cause a switch during development to the besylate salt. (See "Review of Original NDA" for NDA# 19-787 of 10.10.1990, obtainable from FDA under Freedom of Information

Act). The stability and tableting issues/causes are not publicly disclosed in the information available from the FDA.

The present invention relates to the discovery of a novel derivative of amlodipine, the use thereof, and methods of making the same. Specifically, the present invention provides a compound of the following formula (1):



or a pharmaceutically acceptable salt thereof.

The compound of formula (1) is useful as a calcium channel blocker and thus further aspects of the invention relate to a pharmaceutical composition comprising an effective amount of a compound of formula (1) or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable excipient as well as a method of treating angina or hypertension by administering to a patient in need thereof an effective amount of a compound of formula (1) or a pharmaceutically acceptable salt thereof. Further, the present invention can be used in combination with amlodipine as a pharmaceutically active ingredient composition. The compound of formula (1) can be made by a process that comprises reacting amlodipine or a salt thereof with a carbonyl-activated maleic acid compound.

Fig 1 shows the ^1H -NMR spectrum for the material of Example 1.

The compound of formula (1) can be described as (Z)-4-[(2-{[4-(2-chlorophenyl)-3-(ethoxycarbonyl)-5-(methoxycarbonyl)-6-methyl-1,4-dihydro-2-pyridinyl]methoxy}ethyl)amino]-4-oxo-2-butenoic acid. It is understood that the compound represented by formula (1) may exist as the free acid form or as the corresponding zwitter ion form and that while both forms are included within the meaning of the structural formula, for simplicity sake, only the free acid form is shown. Further, while the compound of formula (1) is referred to in the singular, it

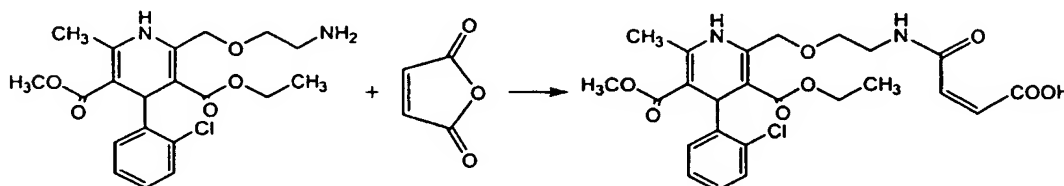
should be understood that the compound can exist as one of two isomers caused by a chiral center on the 1,4-dihydropyridine ring or as a mixture of isomers: all are embraced by the singular "compound."

The compound of formula (1) can be in the form of a salt and is typically a pharmaceutically acceptable salt. Salts include those formed with a metal cation such as an alkali metal cation; those formed with ammonia or an amine compound including mono-, di-, or tri-alkylamine compounds and ring amine compounds; or with an acid. More specifically, metal salts include sodium, potassium and lithium salts of the compound of formula (1). Ammonia and amine salts include salts made with ammonium, methylamine, dimethylamine, triethylamine, pyridine, and amlodipine. Suitable acid salts include inorganic and organic acids such as hydrochloric, sulfuric, phosphoric, acetic, propionic, maleic, fumaric, tartaric, benzoic, methane sulfonic, and benzene sulfonic acid. Salts can also be formed with ambivalent compounds such as aminoacids, e.g. glycine or alanine. Preferred salts include salts made with a pharmaceutically acceptable acid, especially maleic acid. Another preferred salt is the salt formed with amlodipine and the compound of formula (1), especially in a 1:1 molar ratio of the compound of formula (1) with amlodipine.

The compound of formula (1) and its salts are normally solid at room temperature and can be crystalline or amorphous. The crystalline forms include anhydrate forms, hydrated forms and solvate forms. The compound may be isolated and thus of relatively high purity, typically greater than 50 wt % pure, preferably greater than 75 weight % pure, more preferably greater than 95 weight % pure. However, relatively impure forms are also included as are dissolved forms.

The compound of formula (1) can be made by reacting amlodipine or a salt thereof with a carbonyl-activated maleic acid compound. The reaction is essentially an amidation reaction and thus is favored by the presence of an acid catalyst, elevated temperature, etc., and such other amidation conditions as are well known by workers skilled in the art. A "carbonyl-activated maleic acid compound" means maleic acid or a derivative thereof that has a sufficiently activated carbonyl group to facilitate the amidation reaction with amlodipine. In some embodiments the carbonyl activation is achieved by the presence of an acid catalyst, typically a Lewis acid such as aluminium chloride or phosphoric acid. However, the preferred embodiment is to use maleic acid anhydride which provides an activated carbonyl group without the necessity of a

catalyst. Maleic acid per se and in the absence of a catalyst or activator is not a carbonyl-activated maleic acid compound and will not readily form a compound of formula (1) even if placed in the presence of amlodipine. The reaction with maleic acid anhydride is set forth below.



In general, the formation reaction of the compound of formula (1) can be carried out by bringing amlodipine free base or a salt thereof and the activated-carbonyl maleic acid compound into intimate contact with each other. Preferably, the reaction is carried out at an elevated temperature such as 25 - 100°C, more typically 35 - 50°C, and in an appropriate solvent. Among solvents suitable for the addition reaction are polar aprotic solvents, for example N,N-dimethylformamide, alcohols such as ethanol and isopropanol, esters such as ethyl acetate, and hydrocarbons such as toluene. The amlodipine and carbonyl-activated maleic acid compound are normally combined in approximately stoichiometric ratios, namely 0.9:1 to 1:0.9. However, excess amlodipine may advantageously be used in the case where the amlodipine salt of the compound of formula (1) is desired. Also, in cases where a mixture of amlodipine and a compound of formula (1) is desired, as discussed more fully hereinafter, a large molar excess of amlodipine to activated-carbonyl maleic acid compound may be used, e.g. up to 50:1, more typically up to 20:1, and generally 2:1 to 10:1 of amlodipine to carbonyl-activated maleic acid compound on a molar basis. Also, in this embodiment, a non-activated-carbonyl maleic acid may be simultaneously provided along with the activated carbonyl maleic acid compound to form a mixture of amlodipine maleate salt and a compound of formula (1).

Amlodipine free base may be prepared according to the procedures generally outlined in patent No U.S. 4,572,909. Another useful synthesis scheme for making amlodipine or salts thereof in good yields and purity via a phthalimidoamlodipine

intermediate is described in commonly-owned provisional application serial No. 60/258,613, filed December 29, 2000, the entire contents of which are incorporated herein by reference, and in commonly-owned co-pending U.S. patent application serial No. 09/809,351, filed on March 16, 2001, and entitled "Process for Making Amlodipine, Derivatives Thereof, and Precursors Therefor," the entire contents of which are incorporated herein by reference. Maleic acid and its anhydride as well as acid catalysts are all commercially available.

The compound (1) may be isolated from the reaction medium by conventional methods such as evaporation or precipitation, and may be purified by crystallization, for example at reflux temperature in an appropriate solvent, for example an ester such as ethyl acetate, an alcohol such as propan-2-ol, or a ketone such as acetone. The stereoisomers may be separated by crystallization or chromatography, optionally in the form of a salt, for example as salt with an optically active base or acid by methods generally known in the art.

Treatment of compound (1) with an equivalent amount of an acid such as maleic acid optionally followed by an isolation step such as precipitation, evaporation or lyophilization, produces an acid addition salt of the compound of formula (1) with the acid. Other salts of compound (1) may be formed by reaction with an equivalent amount of a base, such as for example sodium hydroxide to form a sodium salt of the compound of formula (1).

The compound of formula (1) and its pharmaceutically acceptable salts are useful calcium channel blockers and thus can be used to treat any cardiac condition that would be benefited by administration of a calcium channel blocker. Additionally, the compound of formula (1) is convertible to amlodipine by hydrolysis of the amide bond. Hydrolysis of the amide bond can occur in vivo, e.g. by metabolism in the body after administration. Accordingly, the compound of formula (1) and its pharmaceutically acceptable salts can be used as a "pro-drug" for amlodipine and thus can be used in the same fashion and are useful in treating the same cardiac conditions as amlodipine.

In particular, the compound of formula (1) and its pharmaceutically acceptable salts can be used to treat or prevent hypertension or angina by administering an effective amount to a patient in need thereof. The specific form of angina is not particularly limited and specifically includes chronic stable angina pectoris and vasospastic angina (Prinzmetal's angina). The compound can be administered by any

suitable route including orally or parenterally. The "patients" intended to be treated include human and non-human animals especially non-human mammals.

The compound is usually administered as part of a pharmaceutical composition. Accordingly, a further aspect of the invention is a pharmaceutical composition for treating or preventing hypertension or angina that comprises an effective amount of a compound of formula (1) or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable excipient. Excipients include any inert or non-active material used in making a pharmaceutical dosage form. For example, tablet excipients include, but are not limited to, calcium phosphate, cellulose, starch or lactose. Capsules such as those made of gelatin, may contain or carry the compound of formula (1) or a pharmaceutically acceptable salt thereof alone or in admixture with other excipients. Liquid dosage forms are also included such as oral liquids in the form of liquors or suspensions, as well as injectable solutions. The pharmaceutical composition may be formulated for transdermal administration in the form of a patch. All of the above-described pharmaceutical compositions may optionally contain one or more of each of the following excipients: carriers, diluents, colorants, flavoring agents, lubricants, solubilizing agents, disintegrants, binders and preservatives.

The pharmaceutical composition is normally provided in a unit dose. A unit dose is typically administered once or twice daily, more typically once daily. In the case of a transdermal patch, the unit dose (one patch) is generally applied at least once a month, more commonly at least once a bi-week, and typically once a week. An effective amount of the compound of formula (1) or a pharmaceutically acceptable salt thereof in a unit dose for treating or preventing hypertension or angina is generally within the range of 1 to 100 mg, typically 1 to 50 mg, more typically 1 to 20 mg. In solid oral dosage forms (tablets, capsules, etc.), the pharmaceutical composition typically contains about 1, 2.5, 5.0, or 10 mg of the compound of formula (1) or a pharmaceutically acceptable salt thereof. For simplicity, all amounts refer to the corresponding amount of free base provided to the composition.

Another embodiment of the invention relates to the use of a mixture of the compound of formula (1) or a pharmaceutically acceptable salt thereof with amlodipine or a pharmaceutically acceptable salt thereof. The combination of these two pharmaceutically active agents can form a useful pharmaceutically active ingredient composition. Generally, the pharmaceutically active ingredient

composition comprises (a) 100 parts by weight of amlodipine or a pharmaceutically acceptable salt thereof and (b) about 0.1 to about 1000 parts by weight, usually 0.5 to 500 parts by weight, more typically 2 to 100 parts by weight of a compound of formula (1) or a pharmaceutically acceptable salt thereof. The amlodipine is preferably in the form of an acid addition salt, especially the maleate salt. The compound of formula (1) is preferably an acid addition salt, especially the maleate salt, or an amlodipine salt or a mixture thereof. The blend may be obtained directly by controlling the ratio of carbonyl-activated maleic acid compound to non-carbonyl-activated maleic acid and/or to the amount of amlodipine. Alternatively, the pharmaceutically active ingredient composition can be formed by blending the amlodipine compound with the compound of formula (1) (or their respective salt forms, etc.) in the desired ratio.

The pharmaceutically active ingredient composition can be used in like manner as the compound of formula (1) to form a pharmaceutical composition for treating hypertension or angina. Specifically, such a pharmaceutical composition comprises an effective amount of the pharmaceutically active ingredient composition and a pharmaceutically acceptable excipient as previously described. Similarly the unit dose contains between 1 and 100 mg, typically 1 to 50 mg, more typically 1 to 20 mg and specifically the solid oral dosage forms (tablets, capsules, etc.) typically contain about 1, 2.5, 5.0, or 10 mg of the pharmaceutically active ingredient composition. For simplicity the stated amounts refer to the weight corresponding to the sum of the free base of the amlodipine and the compound of formula (1).

The pharmaceutically active ingredient composition per se or in the form of a pharmaceutical composition can be used to treat or prevent hypertension or angina by administering an effective amount to a patient in need thereof.

All of the pharmaceutical compositions described above can be made by known methods and techniques. For example, the tablets can be made by dry granulation/direct compression or by a classical wet granulation method. Similarly, capsules can be made by blending the ingredients and filling the capsule. A suitable pharmaceutical composition for the above-described pharmaceutically active ingredient composition, having good stability can be obtained by selecting the excipients so as to have a pH of less than 7.0, when measured as a 20 wt % aqueous slurry, as is more fully described in commonly-owned co-pending U.S. patent application serial No. 09/809,346, filed on March 16, 2001, and entitled

“Pharmaceutical Compositions Comprising Amlodipine Maleate,” the entire contents of which are incorporated herein by reference.

Another use of the amlodipine maleamide of formula (1) is as a reference standard or reference marker for evaluating the purity of amlodipine maleate and pharmaceutical compositions comprising amlodipine maleate as is more fully described in commonly-owned U.S. patent application serial No. 09/809,347, filed on March 16, 2001, and entitled “Reference Standard For Determining The Purity or Stability of Amlodipine Maleate and Processes Therefor” the entire contents of which are incorporated herein by reference.

The following Examples illustrate the invention.

Example 1 - preparation of the compound of formula (1)

5 g of amlodipine was dissolved in 50 ml of ethyl acetate and heated to 60 °C. To this mixture was added 1.15 g of maleic anhydride and the mixture was shaken until the solution was clear. The mixture was cooled to room temperature and left overnight. The mixture was evaporated to dryness and subsequently dried in a high vacuum oven at 25 °C for 3 hours leaving a yellow solid.

Yield: 6.1 g (99 %)

Mp: 83 °C - 86 °C

Purity: greater than 95 % (HPLC)

¹H-NMR spectrum:

The ¹H-NMR spectrum was measured at 303 K on a Bruker Avance-400 in deuterated dimethylsulfoxide at 400 MHz. The spectrum is shown on Fig. 1.

δ assignment

| | | |
|----|------|---|
| | 1.12 | (t, 3H, $J_{11,12}=7.0\text{Hz}$, 12-H ₃) |
| 5 | 2.31 | (s, 3H, 15-H ₃) |
| | 3.44 | (bq, ~2H, 9-H ₂) |
| | 3.52 | (s, ~3H, 14-H ₃) |
| | 3.58 | (bt, 2H, 8-H ₂) |
| | 3.99 | (m, ~2H, 11-H ₂) |
| 10 | 4.62 | (AB q, 2H, 7-H ₂) |
| | 5.32 | (s, 1H, 4-H) |
| | 6.27 | (d, ~1H, $J_{4'',5'}=12.4\text{Hz}$, 4''-H) |
| | 6.43 | (d, ~1H, $J_{4'',5''}=12.4\text{Hz}$, 5''-H) |
| | 7.13 | (dt, 1H, $J_{3',4}=J_{4',5}=7.7\text{Hz}$, $J_{4',6}=1.6\text{Hz}$, 4'-H) |
| 15 | 7.23 | (dt, 1H, $J_{4',5}=J_{5',6}=7.7\text{Hz}$, $J_{3',5}=1.0\text{Hz}$, 5'-H) |
| | 7.28 | (dd, 1H, $J_{3',4}=7.7\text{Hz}$, $J_{3',5}=1.0\text{Hz}$, 3'-H) |
| | 7.34 | (dd, 1H, $J_{4',6}=1.6\text{Hz}$, $J_{5',6}=7.7\text{Hz}$, 6'-H) |
| | 8.49 | (s, ~1H, 1-H) |
| 20 | 9.24 | (bt, ~1H, 9'-NH) |

Example 2 - Preparation of a mixture of amlodipine maleate and amlodipine amide

5 g of amlodipine was dissolved in 50 ml of ethyl acetate at 60°C. To the solution, 1.28 g of maleic acid and 0.12 g of maleic acid anhydride were added and the mixture was shaken until clear. The mixture was slowly cooled to room temperature during which time a solid precipitated. The solid was filtered off and washed with 10 ml of ethyl acetate. After drying in a vacuum oven at 35°C for 18 hours, 5.55 g of a solid was obtained.

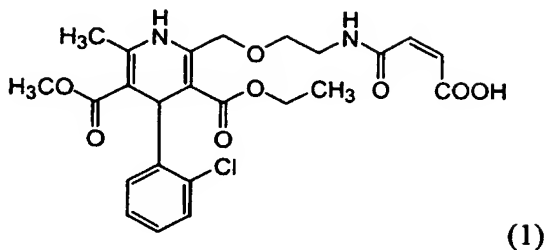
According to HPLC analysis, the content of the compound of formula (1) related to amlodipine maleate was 1.8 %.

The invention having been described, it will be readily apparent to those skilled in the art that further changes and modifications in actual implementation of

the concepts and embodiments described herein can easily be made or may be learned by practice of the invention, without departing from the spirit and scope of the invention as defined by the following claims.

CLAIMS

5 1. A compound of formula (1)



10 or a pharmaceutically acceptable salt thereof.

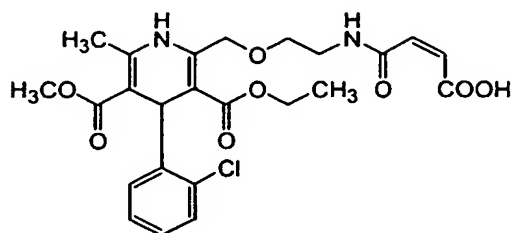
2. The compound according to claim 1, wherein said compound is an alkali metal salt, an amine salt or an acid addition salt.

15 3. The compound according to claims 1 or 2, wherein said compound is an amine salt.

4. The compound according to claim 3, wherein said amine salt is an amlodipine salt of said compound.

20 5. The compound according to claims 1 or 2, wherein said compound is a maleate salt.

6. A pharmaceutical composition for treating angina or hypertension comprising an effective amount of a compound of formula (1)



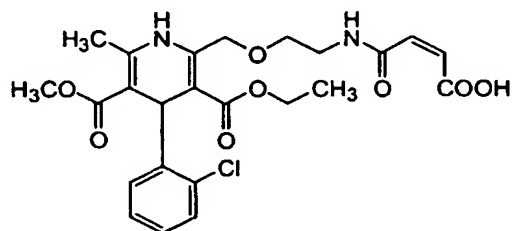
(1)

or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable excipient.

7. The pharmaceutical composition according to claim 6, wherein said compound of formula (1) is in a pharmaceutically acceptable salt form and said composition is in a unit dose form.

8. The pharmaceutical composition according to claims 6 or 7, wherein said pharmaceutically acceptable salt is a maleate salt and said compound of formula (1) is contained in an amount corresponding to 1 to 100 mg.

9. A process which comprises:
reacting amlodipine or a salt thereof with a carbonyl-activated maleic acid compound to form a compound of formula (1) or a salt thereof:



(1).

10. The process according to claim 9, wherein said carbonyl-activated maleic acid compound is maleic acid anhydride.

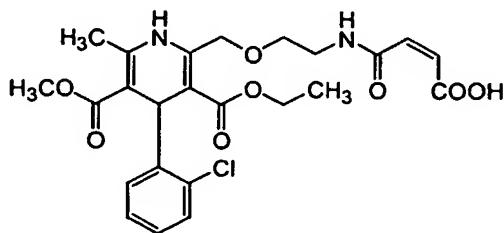
11. The process according to claim 9, wherein said carbonyl-activated maleic acid compound is maleic acid in the presence of an acid catalyst.

12. The process according to claim 11, wherein said acid catalyst is a Lewis acid.

13. The process according to any of the claims 9-12, wherein said reacting step is carried out in a solvent.

14. A process for treating or preventing angina or hypertension which comprises administering an effective amount of the compound/composition according to any of the claims 1-8 to a patient in need thereof.

15. A pharmaceutically active ingredient composition comprising amlodipine or a pharmaceutically acceptable salt thereof and a compound of formula (1)



or a pharmaceutically acceptable salt thereof.

16. The composition according to claim 15, wherein said composition comprises 100 parts by weight of said amlodipine and 0.1 to 1000 parts by weight of said compound of formula (1).

17. The composition according to claims 15-16, wherein said composition comprises said compound of formula (1) in an amount of 0.5 to 500 parts by weight.

18. The composition according to any of the claims 15-17, wherein said composition comprises 100 parts of amlodipine maleate and 2 to 100 parts of the maleate salt, the amlodipine salt, or both salt forms, of said compound of formula (1).

19. A pharmaceutical composition for treating or preventing angina or hypertension comprising an effective amount of the pharmaceutically active ingredient composition according to any of the claims 15-18 and a pharmaceutically acceptable excipient.

20. The pharmaceutical composition according to claim 19, wherein said pharmaceutical composition is a unit dose form.

21. The pharmaceutical composition according to claim 20, wherein said effective amount of said pharmaceutically active ingredient composition is within the range of 1 to 20 mg.

22. A process for treating or preventing angina or hypertension which comprises administering to a patient in need thereof an effective amount of a pharmaceutically active ingredient composition according to any of the claims 15-18, and/or a pharmaceutical composition according to any of the claims 19-21.

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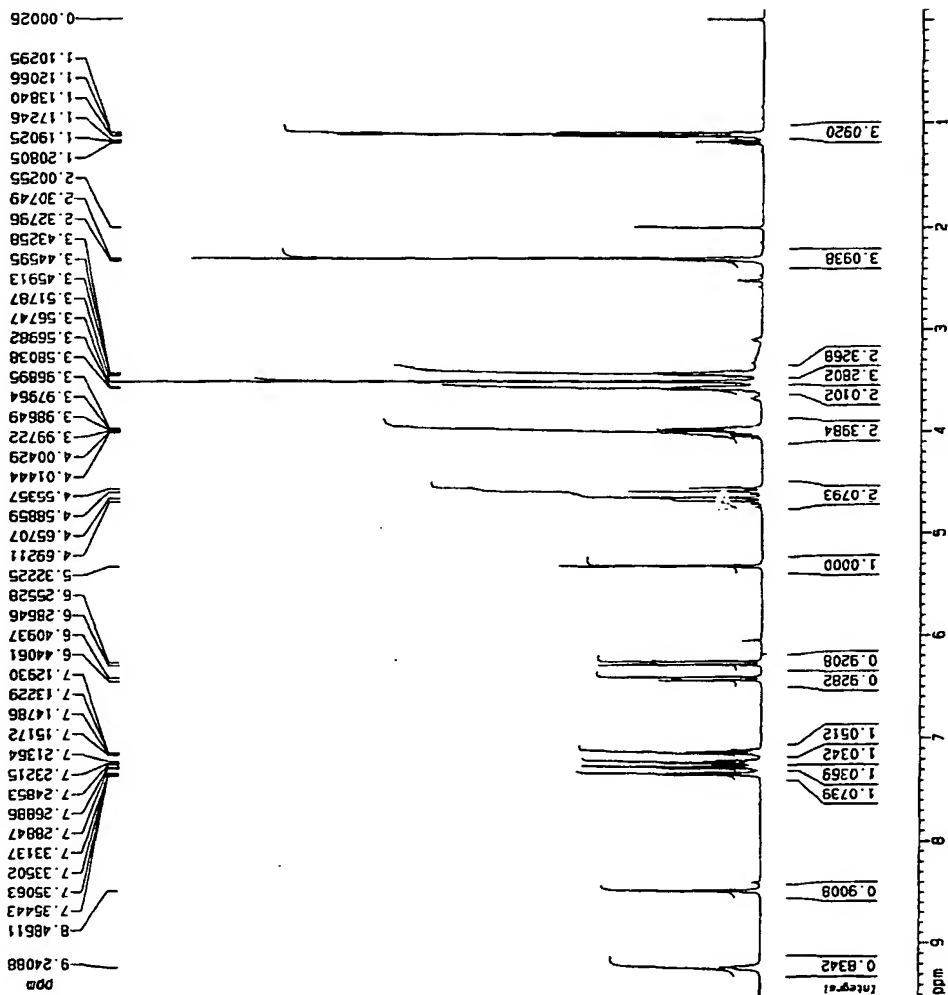


Fig. 1

INTERNATIONAL SEARCH REPORT

International Application No

PCT/NL 01/00604

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D211/90 A61K31/44 A61P9/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|--|-----------------------|
| A | US 4 572 908 A (CAMPBELL SIMON F ET AL) 25 February 1986 (1986-02-25) cited in the application example 9 ----- | 1,6,14, 15,19,22 |



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
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- *P* document published prior to the international filing date but later than the priority date claimed

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Date of the actual completion of the international search

26 April 2002

Date of mailing of the international search report

13/05/2002

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

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